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**Miscreant myeloproliferative disorder stem cells.**

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**Public Summary:**

**Scientific Abstract:**

Myeloproliferative disorders (MPDs), typified by robust marrow and extramedullary hematopoiesis, have a propensity to progress to acute leukemia. Although the hematopoietic stem cell (HSC) origin of MPDs was suggested over 30 years ago, only recently the HSC-specific effects of MPD molecular mutations have been investigated. The pivotal role of BCR-ABL in chronic myeloid leukemia (CML) development provided the rationale for targeted therapy, which greatly reduced mortality rates. However, BCR-ABL inhibitor-resistant CML HSCs persist that may be a reservoir for relapse. This has provided the impetus for investigating molecular mechanisms governing the production of recalcitrant HSC. Comparatively little was known about the molecular events driving BCR-ABL-negative MPDs until seminal studies revealed that a large proportion of MPD patients harbor a JAK2-activating point mutation, JAK2V617F. Although JAK2 activation appears to be central to BCR-ABL-negative MPD pathogenesis, its effects may be cell type and context specific. Recent evidence suggests that acquired mutations misdirect differentiation and survival of the MPD-initiating stem cell resulting in the production of aberrant self-renewing progenitors that subvert the microenvironment leading to leukemia stem cell generation and leukemic transformation. Thus, combined therapies targeting aberrant molecular pathways may be required to redirect miscreant MPD stem cells.

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